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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	13

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/651,846	HLA ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 18-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 18-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

15)☒ Notice of References Cited, PTO-892

☐ Interview Summary, PTO-413, Paper No(s). ___

DETAILED ACTION

1 The restriction requirement set forth 4/10/01 is moot in view of applicant's cancellation of claims 1-17 and 21-32.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite for the language "one or more of" since it is not clear whether applicants are claiming a single oligonucleotide that comprises two or more of the specifically claimed SEQ ID NOS. or whether a composition is claimed having a combination of one or more oligonucleotide sequences within the different SEQ ID NOS. (ie., taking a portion of more than one of the SEQ ID NOS. and combining them to form a new sequence).

Claim 20 is indefinite for the language "analog" and "derivative" because neither the specification nor the art define what the metes and bounds of an analog or a derivative are such

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 18 is drawn to a composition comprising an antisense oligonucleotide that inhibits in vivo expression of at least one EDG gene. The claim thus reads broadly on a broad scope of possible EDG genes from any whole organism (ie. any species) and antisense compositions to those genes.

The specification as filed teaches antisense to the human EDG-1, EDG-3 and EDG-5 receptors. The specification does not disclose antisense to any other EDG gene from human or any other species.

The claims thus read on a breadth of possible EDG genes from any organism of which the specification as filed does not teach a representative number of species. The sequence structure of an antisense is critical to the ability of the antisense to bind an accessible region of a target said gene. The limited examples in the specification of antisense to human EDG-1 and EDG-3 are

not representative of the scope of possible EDG genes from any organism and antisense to said genes. In particular, the claims recite the limitation of the claimed antisense to function in vivo. Due to the high level of unpredictability in the art for administration of antisense to cells in whole organisms (see the scope of enablement rejection below), the structure of antisense which function in vivo would have been all the more unpredictable to one skilled in the art. Antisense which function in a whole organism have the added burden of unpredictable factors such as degradation, toxicity, etc. As such, one skilled in the art would not have been in possession of a representative number of such antisense to any possible EDG receptor as broadly claimed.

6. Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense to EDG in cells in culture (*in vitro*), does not reasonably provide enablement for antisense to EDG for function in cells in whole organisms (*in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 18-20 are drawn to antisense compositions to EDG for use *in vivo*. The claims read on use of any anti-EDG from any organism.

The specification as filed teaches by way of example (in Table 1, page 36) three antisense

Stress Fiber and VE-Cadherin cells

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for

[illegible] molecule will be accessible *in vivo*, effective antisense molecules must be found

empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claim 18 is rejected under 35 U.S.C. 102(a) as being anticipated by Goetzl et al. (Proc. Of the Association of Am. Physicians, May-June 1999, 111 (3) p259-69).

Claim 18 is drawn to antisense oligonucleotides to EDG receptor.

Goetzl et al. teach antisense to Edg-2 and Edg-4. Goetzl et al. thus anticipate the claimed invention.

9. Claim 18 is rejected under 35 U.S.C. 102(a) as being anticipated by Goetzl et al. (J. Of Immunology, Feb. 15, 1999, 162 (4) p2049-56).

Claim 18 is drawn to antisense oligonucleotides to EDG receptor.

Goetzl et al. teach antisense to Edg-3 and Edg-5. Goetzl et al. thus anticipate the claimed invention.

instant claims because of the closed language claiming the specific SEQ ID Nos

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

ANDREW WANG